

Remarks***Restriction Requirement***

Applicants request reconsideration of the Examiner's decision to restrict the present claims to treating obesity. Applicants have a special technical feature, namely that the claimed compounds are active at the 5HT₂ receptor in Assays (1) and (2) (See specification, page 17, last line to page 19, last line). On the basis that all the disorders recited in claim 28 are known to be associated with 5HT₂-receptor malfunction, there is unity of invention for the presently claimed compounds under PCT Rule 13.2. The presently claimed compounds are capable of modulating the 5HT₂ receptor and therefore treating the noted disorders and making a technical contribution over the prior art.

As far as using different formulations for different disease states is concerned, it is commonly acknowledged that the optimal treatment for victims of stroke is an I.V. administered therapy for rapid action and immediate access to the site of injury. On the other hand, treatment of drug addicts and some schizophrenics where patients cannot be trusted to take their medication as prescribed is often by depot injections. Thus a 5-HT₂ receptor agonist may be used under different formulation requirements for use in different indications, but this does not affect the unity of invention of the claimed compounds.

In addition, the Examiner's argument on the applicability of obesity prior art to the aspect of the claims directed to stroke or schizophrenia is not well-founded. The Examiner has not referenced any prior art that discloses that the present compounds were active at the 5HT₂ receptor, and therefore useful in treating the claimed disorders. Therefore, as the Examiner has not established a basis for the lack of unity of invention for the claimed compounds, applicants respectfully request withdrawal of the restriction requirement, especially as directed to the claimed disorders.

Rejections for Indefiniteness

Applicants have deleted the term prodrug from claim 1. With respect to claim 29, applicants respectfully request reconsideration of this rejection based on the above request to withdrawal of the restriction requirement, especially as directed to the claimed disorders.

Anticipation Rejection Over US-3853878 (Jonas)

In Jonas, the active compounds disclosed (see column 1, lines 10 to 25; column 2, lines 16 to 27; and Examples 1 to 4) all contain a carboxamidine group, and are, therefore, different than the presently claimed compounds. The compounds cited by the Examiner are only intermediates and are not proposed for any medical use. Therefore, these intermediate compounds cannot anticipate or render obvious the pending claims.

Anticipation Rejection Over US-5854245 (Duggan)

Applicants contend that the intermediates in columns 43, 44, 47 and 48 of Duggan cannot anticipate or render the present claims obvious. Compounds of Duggan 9-8, 9-9, 9-12 and 9-13 all contain an amido group bound to the phenyl ring of the indole. In contrast, the presently claimed compounds for R₄ to R₇ do not recite amido. Moreover, the R₆ substituent in the presently claimed compounds is not selected from a group which binds via a carbonyl group. In compounds 9-8, 9-9, 9-10, 9-11, 9-12 and 9-13 of the prior art, the "R₆-position" is always occupied by a substituent bound via a carbonyl group. With regard to compounds 9-10 and 9-11, there is also a t-butyloxycarbonyl group on the exposed N atom of the pyrazine ring. This protecting group is bound to the atom through the COO group. Accordingly, these cannot anticipate or suggest the presently claimed compounds.

Obviousness Rejection Over Med. Chem. Res. 3:240-248, 1993 (Mokrosz)

Applicants wish to note that this paper was cited during International Preliminary Examination and they satisfied the (European) Examiner of the inventive step of the claims as filed over this document in combination with EP-0572863. The US Examiner has, however, raised a further objection in view of this document alone.

The Examiner considers that the substituted-phenyl ring compounds now claimed are obvious. Applicants have, however, been able to show an unexpected advantage of the presently claimed compounds with comparative data, which show the weak efficacy of the unsubstituted compounds. All the substituted compounds have EC₅₀ values that are approximately 7 to 300 fold lower than the unsubstituted examples of the present invention. The presently claimed compounds therefore possess greater agonist potency. These data are set out in Exhibit 1, adapted from Table 2, at page 19 of the specification. The superiority of the presently claimed compounds could not have been predicted from the prior art and, therefore, the

claimed subject-matter is non-obvious. Accordingly, applicants request withdrawal of all outstanding rejections.

Respectfully submitted,

Date December 6, 2002

By



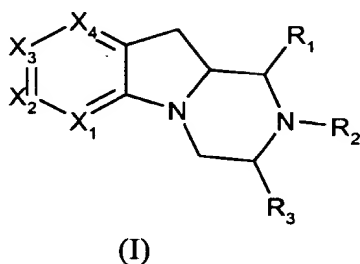
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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

Version With Markings to Show Changes Made

1. (Amended Twice) A pharmaceutical composition comprising a
chemical compound of formula (I):



wherein:

R₁ to R₃ are independently selected from hydrogen and lower alkyl;

X₁ is selected from N and C-R₄;

X₂ is selected from N and C-R₅;

X₃ is selected from N and C-R₆;

X₄ is selected from N and C-R₇;

R₄, R₅ and R₇ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkoyl, aryloyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino, nitro, cyano, carboalkoxy, carboaryloxy and carboxy; and

R₆ is selected from hydrogen, halogen, alkyl, aryl, aryloxy, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino and cyano;

with the proviso that R₄ to R₇ are not all selected as hydrogen,

or a pharmaceutically acceptable salt, or addition compound ~~[or prodrug]~~ thereof; in combination with a pharmaceutically acceptable carrier or excipient.